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Case report

Cefiderocol for treatment of an empyema due to extensively drug-resistant *Pseudomonas aeruginosa*: Clinical observations and susceptibility testing considerations

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ABSTRACT

Cefiderocol is a novel siderophore cephalosporin antibacterial with activity against carbapenem-resistant Gram-negative bacteria including *Pseudomonas aeruginosa*. We report a medically complex patient treated with compassionate use cefiderocol for an empyema caused by extensively drug-resistant *P. aeruginosa* as well as clinical considerations for cefiderocol use based on our findings. We observed a potential discordance in cefiderocol susceptibility testing results depending if disk diffusion or iron-depleted cation-adjusted Mueller Hinton Broth dilution is used. Furthermore, interpretative criteria differ between the Clinical Laboratory Standards Institute and United States Food and Drug Administration for *P. aeruginosa*, which makes cefiderocol interpretation potentially challenging for clinicians. We may have also observed selective pressure from prior cefiderocol exposure given the respective increases and decreases in MIC values and zone diameters for *P. aeruginosa* isolates following cefiderocol treatment. Additional data are needed to further describe cefiderocol use, susceptibility testing, and resistance development as real-world clinical use expands.

Introduction

Cefiderocol, a novel siderophore cephalosporin, utilizes a 'Trojan horse' active transport mechanism via specialized iron transporters to ultimately inhibit cell wall synthesis [1,2]. This unique mechanism allows cefiderocol to evade efflux pumps and porin channels. Cefiderocol also demonstrates stability to several serine- and metallo-beta-lactamases. Based on these properties, cefiderocol exhibits activity against several multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative bacteria [1–3].

Cefiderocol is currently approved by the United States (US) Food and Drug Administration (FDA) for treatment of complicated urinary tract infections (cUTI) based on a randomized, double-blind, non-inferiority trial that demonstrated non-inferiority between cefiderocol and imipenem-cilastatin [4,5]. However, limited data exist to describe real-world cefiderocol use for the treatment of MDR and XDR Gram-negative bacterial infections [6–11]. Thus, we describe our experience with compassionate use cefiderocol for a patient with an empyema caused by XDR *Pseudomonas aeruginosa* to add to the growing body of real-world data as clinical use expands.

Case report

A 45-year-old, 67 kg female presented to our institution for higher level management of an esophageal-pleural fistula. A detailed summary of relevant treatment course is presented in Table 1. Her history was significant for hemangioblastoma requiring several neurosurgical interventions. She presented to a referring hospital for worsening neurological symptoms and underwent an elective craniotomy for cyst repair, which was complicated by a left-sided hydropneumothorax requiring chest tube placement and leukocytosis. Analysis of the pleural fluid was consistent with an empyema and the pleural fluid culture grew *Candida albicans*. Her course was further complicated by an esophageal perforation requiring laparotomy and perforation

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Table 1
Clinical, microbiological, and antimicrobial treatment course during hospitalizations and rehabilitation.

Admission	Treatment course day	Summary of significant events during clinical course	Antimicrobial regimens
Hospital #1, admission #1	1	• Elective craniotomy for repair of cyst in posterior fossa	• Cefazolin 1 g (SSI prophylaxis)
	3	• CT thorax revealed large left-sided hydropneumothorax • Left-sided chest tube placed with pleural fluid culture positive for *Candida albicans* • Exploratory laparotomy revealed esophageal perforation • Esophageal rupture repair • Placement of a GT and JT • Started on antimicrobials for empyema	• Meropenem 1 g intravenously every 8 h over 0.5h • Vancomycin per pharmacy protocol • Micafungin 100 mg intravenously every 24h
	8	• Chest x-ray revealed a left-sided pneumothorax requiring chest tube placement	
	13	• Gastrografin swallow evaluation complicated by aspiration of contrast in left main bronchus • EGD revealed persistent esophageal injury requiring esophageal stent	
	15	• Tracheostomy placed due to persistent dysphagia	
Rehabilitation facility	23	• Discharged to rehabilitation facility	
Hospital #1, admission #2	33	• Admitted for acute respiratory failure • CT thorax revealed an esophageal-pleural fistula • Pleural fluid cultures from left chest tube positive for *Pseudomonas aeruginosa*	• Ceftazidime-avibactam 2.5 g IV q8 h over 2h • Fluconazole 400 mg IV q24h • Amikacin 1000 mg IV q24h
	34	• *P. aeruginosa* susceptibilities revealed MDR isolate (susceptibilities in Table 2) • Transferred to our institution for higher level management of the esophageal-pleural fistula	
Hospital #2 admission #1	35	• Antimicrobial regimen changed • Compassionate use cefiderocol requested • OR for EGD esophageal stent replacement • Leukocytosis (WBC 14100/uL); afebrile	• Ceftazidime-avibactam 2.5 g IV q8 h over 2h • Fluconazole 400 mg IV q24h • Polymyxin B 1,500,000IU load then 1,000,000IU IV q12h
	40	• OR for video-assisted thoracoscopic surgery with left lung thoracotomy decortication and esophageal rupture repair with a muscle flap coverage • Leukocytosis (WBC 19900/uL); afebrile	
	42	• Antimicrobial regimen changed (cefiderocol arrived/initiated) • Leukocytosis (WBC 27000/uL); low grade fever (38.2 degrees Celsius)	• Cefiderocol 2 g IV q8 h over 3h • Fluconazole 400 mg IV q24h
	46	• Left chest tube removed due to improvement in pleural effusions on CT thorax • Leukocytosis (WBC 17600/uL); afebrile	
	56	• Worsening respiratory status and CT thorax revealed loculated left and right pleural effusions • Right and left chest tubes placed • Leukocytosis (WBC 11200/uL); afebrile	
	59	• Pleural fluid cultured from left and right chest tube with no growth • Left chest tube removed • WBC 9000/uL; afebrile	
	63	• Right chest tube removed • WBC 9300/uL; afebrile	• Antimicrobial regimen completed
	73	• Increased tracheal secretions • Tracheal aspirate sent for culture • CT thorax demonstrated radiographic improvement of bilateral pleural effusions • Leukocytosis (WBC 11300/uL); afebrile	• No antimicrobials
	76	• Tracheal aspirate culture grew two morphologic variants of *P. aeruginosa* non-susceptible to cefiderocol via disk diffusion • Leukocytosis (WBC 16100/uL); afebrile	
	80	• Two morphologic variants of *P. aeruginosa* sent to reference laboratory for additional testing • Leukocytosis (WBC 19800/uL); afebrile	

Table 1 (*Continued*)

Admission	Treatment course day	Summary of significant events during clinical course	Antimicrobial regimens
	82	• OR for esophageal stent removal • Leukocytosis (WBC 15800/uL); afebrile	
	88	• Patient discharged to rehabilitation • Leukocytosis (WBC 11100/uL); afebrile	
	94	• Two morphologic variants of *P. aeruginosa* tested susceptible to cefiderocol using ID-CAMHB at reference laboratory	

Abbreviations: CT, computed tomography; ID-CAMHB, iron-depleted cation-adjusted Mueller Hinton Broth; EGD, esophagogastroduodenoscopy; GT, gastrostomy tube; g, gram; h, hours; IU, international units; IV, intravenously; JT, jejunostomy; mg, milligram; OR, operating room; q, every; SSI, surgical site infection.

repair with jejunostomy and gastrostomy tube placement. She developed persistent esophageal injury and dysphagia requiring stent and tracheostomy placement, respectively, and was eventually discharged to rehabilitation on day 23, but readmitted ten days later for respiratory failure, leukocytosis, and fever in the setting of an esophageal leak. A computed tomography thorax revealed an esophageal-pleural fistula and a repeat pleural fluid culture from the left chest tube grew XDR *P. aeruginosa* (Table 2). She was transferred to our institution for esophageal-pleural fistula repair and antimicrobial management.

On admission to our institution on day 35, she presented with leukocytosis, but was afebrile. While pursuing compassionate use cefiderocol, she was started on ceftazidime-avibactam, polymyxin B, and fluconazole. She underwent esophageal stent replacement, video-assisted thoracoscopic surgery with left lung thoracotomy and decortication, and esophageal rupture repair with muscle flap placement for surgical management of the esophageal-pleural fistula. Cefiderocol arrived one week after requested, and her antimicrobial regimen was modified to solely fluconazole plus cefiderocol 2 g every 8 h by intravenous infusion over three hours.[4] She had normal renal function with an estimated creatinine clearance of 112 mL/min. Shortly before initiation of cefiderocol, she developed a low-grade fever (38.2 °C), which resolved soon after cefiderocol initiation. Disk diffusion susceptibility testing was performed on the initial *P. aeruginosa* isolate from the pleural fluid, which demonstrated a large zone of inhibition (24 mm) implying cefiderocol susceptibility (Table 2). The isolate was sent to an independent reference laboratory to perform iron-depleted cation-adjusted Mueller Hinton broth (ID-CAMHB) dilution testing, which confirmed susceptibility (Table 2). Cefiderocol interpretative criteria for *Pseudomonas aeruginosa* using both susceptibility testing methods are displayed in Table 3 [12,13]. She completed a total of three weeks of cefiderocol plus fluconazole on day 63 with no observed adverse effects, and responded clinically with leukocytosis resolution and bilateral chest tube removal.

Ten days following completion of cefiderocol, she developed leukocytosis and respiratory symptoms including increased tracheal secretions. A tracheal aspirate culture was obtained, which grew two morphologic variants of XDR *P. aeruginosa*, and both were found to be non-susceptible to cefiderocol by disk

Table 2
Antibacterial susceptibilities of *Pseudomonas aeruginosa* isolates throughout the clinical course.

	Pleural fluid isolate (day 33)		Morphologic variant #1 from tracheal aspirate (day 76)		Morphologic variant #2 from tracheal aspirate (day 76)	
Antibacterial	MIC (mg/L) or KB zone	Qualitative interpretation[f]	MIC (mg/L) or KB zone	Qualitative Interpretation[f]	MIC (mg/L) or KB zone	Qualitative interpretation[f]
Amikacin[a]	16	Susceptible	16	Susceptible	8	Susceptible
Aztreonam[a]	≥32	Resistant	N/A	N/A	N/A	N/A
Cefepime[a]	≥64	Resistant	≥64	Resistant	≥64	Resistant
Cefiderocol[b]	24 mm	Susceptible[g]	17 mm	Intermediate[g]	6 mm	Resistant[g]
Cefiderocol[c]	0.25	Susceptible	0.5	Susceptible	1	Susceptible
Ceftazidime[a]	≥64	Resistant	≥64	Resistant	≥64	Resistant
Ceftazidime-avibactam[d]	≥16/4	Resistant	≥16/4	Resistant	≥16/4	Resistant
Ceftolozane-tazobactam[d]	≥16/4	Resistant	≥16/4	Resistant	≥16/4	Resistant
Ciprofloxacin[a]	≥2	Resistant	≥2	Resistant	≥2	Resistant
Colistin[e]	2	Susceptible	N/A	N/A	N/A	N/A
Gentamicin[a]	≥16	Resistant	≥16	Resistant	≥16	Resistant
Imipenem-cilastatin[a]	≥8	Resistant	N/A	N/A	N/A	N/A
Levofloxacin[a]	≥4	Resistant	N/A	N/A	N/A	N/A
Meropenem[a]	≥8	Resistant	≥8	Resistant	≥8	Resistant
Piperacillin-tazobactam[a]	≥128/4	Resistant	64/4	Intermediate	32/4	Intermediate
Tobramycin[a]	≥16	Resistant	≥16	Resistant	≥16	Resistant

Abbreviations: MIC, minimum inhibitory concentration; KB, Kirby-Bauer disk diffusion; mg/L, milligrams per liter; mm, millimeter.
[a] Automated broth microdilution (MicroScan, Beckman Coulter, Brea, CA, USA).
[b] Kirby-Bauer disk diffusion on unsupplemented standard Mueller-Hinton agar using disks impregnated with 30 micrograms of cefiderocol supplied by Shionogi.
[c] Dilution testing performed by a referral laboratory using iron-depleted cation-adjusted Mueller-Hinton broth.
[d] Gradient diffusion (bioMérieux Inc., Durham, NC, USA).
[e] Broth microdilution (ARUP Labs, Salt Lake City, UT, USA).
[f] Susceptibility data were interpreted according to the Clinical and Laboratory Standards Institute document M100, 29th ed.
[g] At the time of this case, cefiderocol susceptibility data was interpreted according to the following criteria provided by Shionogi (susceptible: ≥18 mm; intermediate: 13–17 mm; resistant: ≤12 mm).

Table 3
Comparison of Cefiderocol Interpretative Criteria for *Pseudomonas aeruginosa*.

	Disk Diffusion (Zone Diameters in mm)[a]			Minimum Inhibitory Concentrations (mg/L)[b]		
	S	I	R	S	I	R
Clinical Laboratory Standards Institute	≥18	13–17	≤12	≤4	8	≥16
United States Food and Drug Administration	≥25	19–24	≤18	≤1	2	≥4

Abbreviations: S, susceptible; I, intermediate; R, resistant.
[a] Using paper disks impregnated with 30 micrograms of cefiderocol on unsupplemented standard Mueller-Hinton agar.
[b] Using iron-depleted cation-adjusted Mueller-Hinton broth.

diffusion. Morphologic variant #1 was intermediate (17 mm) and morphologic variant #2 was resistant (6 mm) to cefiderocol according to Clinical Laboratory Standards Institute (CLSI) as described in Table 2. To further investigate these findings, the isolates were referred to the same independent laboratory for ID-CAMHB dilution testing. Interestingly, both morphologic variant #1 and #2 were found susceptible with a MIC of 0.5 mg/L and 1 mg/L, respectively (Table 2). Given the patient's clinical stability at the time, the culture was presumed to represent colonization, and antibacterials were not initiated. She was eventually discharged to a rehabilitation facility for tracheostomy management without antibacterials.

Since the date of discharge, she has been admitted to both the referring hospital and our institution multiple times for various indications including gastrointestinal bleeding and respiratory management. However, infectious disease consultation recommended to hold antibacterials during these admissions given the lack of a drainable effusion, clinical stability, and presumed colonization.

Discussion

Given the unique mechanism of action and *in vitro* activity against carbapenem-resistant Gram-negative bacteria, cefiderocol's role in therapy may lie in the treatment of infections where limited to no antibacterials exist [1,2,14]. Thus, more real-world data are needed to further evaluate cefiderocol use in this capacity. Currently available data demonstrate conflicting results that have led to multiple uncertainties for clinicians [6–11,15].

While not published yet, preliminary data from two phase 3 trials, APEKS-NP and CREDIBLE-CR, resulted in additional questions regarding cefiderocol use [10,11]. APEKS-NP was a multicenter, randomized, double-blind, parallel-group, non-inferiority study, which compared cefiderocol to dose-optimized meropenem (2 g every 8 h) for nosocomial pneumonia [11]. Based on preliminary results, cefiderocol (n = 148) demonstrated non-inferiority to meropenem (n = 150) for the primary outcome of all-cause mortality at 14 days with rates of 12.4 % and 11.6 %, respectively (treatment difference: 0.8 %, 95 % CI -6.6, 8.2). CREDIBLE-CR was a multicenter, randomized, open-label study to compare cefiderocol (n = 101) versus best-available therapy (n = 49) for carbapenem-resistant infections [10]. All-cause mortality was higher among patients treated with cefiderocol compared to best-available therapy at day 14 (18.8 % versus 12.2 %), day 28 (24.8 % vs 18.4), and at day 49 (33.7 % vs 20.4 %), yet no attributable cause for this difference was identified. Based on these findings, the prescribing information includes a warning for increased risk of all-cause mortality among patients who receive cefiderocol for carbapenem-resistant infections [4], which is presumably its intended patient population.

To date, four case reports have been published describing successful use of cefiderocol for various XDR Gram-negative infections [6–9]. The first case by Edgeworth and colleagues described a 78-year-old female with native aortic valve endocarditis caused by XDR *P. aeruginosa* who was successfully managed with valve replacement and combination antibacterial therapy with cefiderocol, colistin, and meropenem [7]. Cefiderocol was added to preexisting colistin and meropenem on day 83 of the treatment course with valve replacement on day 85. Cefiderocol and colistin were continued for an additional three weeks. Disk diffusion testing was performed on *P. aeruginosa* isolates from blood cultures on day 3 and day 68 with zones of 17.4 mm and 21.3 mm, respectively. The second case by Trecarichi and colleagues described an adult male with ventilator-associated pneumonia and bacteremia caused by XDR *Acinetobacter baumannii* and carbapenemase-producing *Klebsiella pneumoniae* [8]. Compassionate use cefiderocol was started on day 35 in combination with linezolid for 14 days, and the patient was ultimately discharged to a rehabilitation facility without antibacterials or signs and symptoms of infection.

The third case by Stevens and colleagues described a 46-year-old male with an intraabdominal abscess caused by MDR *P. aeruginosa* who was successfully treated with cefiderocol in combination with surgical management [6]. Compassionate use cefiderocol was started on day 73 of the management course in combination with metronidazole for a total of 28 days. The *P. aeruginosa* isolate tested susceptible using ID-CAMHB dilution and disk diffusion testing with a MIC of 0.12 mg/L and zone of 22 mm, respectively. The fourth case by Alamarat and colleagues described a 15-year-old male with chronic osteomyelitis caused by XDR *P. aeruginosa* and extended-spectrum beta-lactamase-producing *K. pneumoniae* [9]. The patient was successfully treated with compassionate use cefiderocol for 14 weeks in combination with a bone implant. The *P. aeruginosa* isolate tested susceptible using both ID-CAMHB dilution and disk diffusion with a MIC of 4 mg/L and zone of 18 mm, respectively. These case reports demonstrate successful clinical outcomes with cefiderocol for infections caused by carbapenem-resistant, cefiderocol-susceptible bacteria. However, cefiderocol initiation was often delayed, patients received several antibacterials prior to or in combination with cefiderocol, and surgical management was commonly performed that may have impacted these patients' outcomes. Interestingly, two patients experienced neutropenia while on prolonged courses of cefiderocol, which was not observed during shorter courses for cUTI [5,7,9]. Regardless, these cases represent real-world, complex patients where cefiderocol use is likely to be considered.

Our case provides additional real-world data describing compassionate use cefiderocol for an empyema due to XDR *P. aeruginosa* in a medically complex patient. However, it is unclear if this patient was successfully treated with cefiderocol for this XDR *P. aeruginosa* empyema in our opinion. She arguably achieved clinical cure because she remained clinically stable from an active infection perspective following three weeks of cefiderocol, yet remained colonized with XDR *P. aeruginosa* demonstrating

microbiological failure. This case is complicated by several surgical procedures, and the potential need for ongoing source control may also still be contributing.

Our experience also raises some important susceptibility testing considerations that clinicians should be aware of. First, cefiderocol MIC testing requires ID-CAMHB [12]. Unlike disk diffusion testing, ID-CAMHB is not yet commercially available, may not be largely familiar to clinical laboratories, and preparation of such media appears logistically complex [12,15].

Second, discordance may exist in the correlation between susceptibility testing methods as well as susceptibility interpretative criteria. While cefiderocol disk diffusion zone diameters have previously demonstrated good correlation with cefiderocol MICs using ID-CAMHB, a poorer agreement has been observed with *P. aeruginosa* compared to other Gram-negative bacteria using these two methods [16]. The US FDA and CLSI both provide interpretative criteria for both disk diffusion and ID-CAMHB dilution; however, interpretive criteria differs making interpretation challenging for clinicians (Table 3) [12,13]. In our case, the two morphologic variants of *P. aeruginosa* from the tracheal aspirate culture yielded inconsistent interpretations for disk diffusion testing using CLSI and FDA criteria. Furthermore, these disk diffusion susceptibility testing results provided contradictory interpretations when compared to the MIC results using ID-CAMHB dilution. Morphologic variant #1 demonstrated a zone diameter of 17 mm, which was determined to be intermediate according to CLSI, yet resistant according to the FDA (Table 2). However, the same variant was determined to be susceptible by ID-CAMHB dilution with a MIC of 0.5 mg/L using both the FDA and CLSI criteria (Table 2). Morphologic variant #2 demonstrated no zone of inhibition (6 mm), yet was deemed susceptible by ID-CAMHB dilution with a MIC of 1 mg/L according to both the FDA and CLSI (Table 2). Given that neither susceptibility testing method is considered the reference method and the potential for discordance to exist between them, susceptibility testing and clinical interpretation may pose a particular challenge for clinicians.

Third, we may have observed selective pressure from prior cefiderocol exposure given the respective increases and decreases in MIC values and zone diameters between the cultured *P. aeruginosa* isolates, which has not reported or observed in the aforementioned cases.[6–9] In the CREDIBLE-CR study, 19 % (15/80) of patients experienced a $\geq$4-fold increase from baseline MIC during cefiderocol treatment, yet only 3 of these isolates were *P. aeruginosa* [17]. Interestingly, Stevens and colleagues reported the same susceptible MIC result (0.12 mg/L) for *P. aeruginosa* before and after 12 days of cefiderocol treatment in their case [6]. Resistance development to cefiderocol is apparently low, and primarily due to mutations in genes related to iron acquisition based on limited data available currently [10,18–21]. Outer membrane iron transporter *piuA* in *P. aeruginosa* is responsible for active transport of cefiderocol, and thus, mutations in the *piuA* gene may confer resistance [19,22]. Previous knockout experiments deleting specific iron transport genes also caused small MIC increases, but remained susceptible to cefiderocol [10]. This may be speculative in our case because the cefiderocol non-susceptible *P. aeruginosa* isolates were obtained from both pleural fluid and tracheal aspirate specimens. Whole genome sequencing was also not performed so it is unknown if these morphologic variants were related.

Cefiderocol represents a potentially safe and effective novel siderophore cephalosporin for XDR *P. aeruginosa* where limited safe and effective antibacterials exist. Further investigations are needed to better characterize cefiderocol use, susceptibility testing methods, and resistance development as real-world clinical use expands.

Ethics

Institutional review board approval was obtained for compassionate use cefiderocol. Informed consent was obtained from the patient for treatment with cefiderocol and for publishing this case.

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This work was carried out as part of our routine clinical practice.

Declaration of Competing Interest

W.D.K. has received grant funding from Melinta and Merck and has served on the advisory board for Theratechnologies, Inc. J.M.S has served on the advisory board for Paratek Pharmaceuticals. All other authors have nothing to disclose.

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